(SEQ ID NO:) was given to this peptide, since, according to 37 C.F.R. §§ 1.821(a)(2), "Those amino acid sequences containing D-amino acids are not intended to be embraced by this definition". A peptide with solely the given abbreviated notation "ri", as defined on page 14, lines 3-5, may include a peptide "written, from left to right, from the C-terminal to the N-terminal amino acid, e.g. the opposite of typical L-peptide notation", which still contains only L-amino acids. As such, this "ri" peptide would require inclusion in the Sequence Listing, but entered as FVFRVNQLVGQF written in the standard N-terminal to C-terminal nomenclature from left to right. This clarification for the retro-inverso peptide in **Table 5**, is justified by the paragraph beginning on page 47, line 9, where a discussion of the results indicated in **Table 5** includes the statements "The D-reverse analog ri-FQGVLQNVRFVF also inhibits in the CAM assay..." (lines 13-14), and "D-reverse analogs of the integrin antagonist peptides are functional *in vivo*..." (lines 16-17). Thus, the insertion of the clarifying "D" distinguishes between a retro-inverso peptide which requires inclusion in the Sequence Listing from one that does not, whereas the context of **Table 5** results clearly identifies this peptide as one that does not require inclusion.

Applicants request entry of this amendment in adherence with 37 C.F.R. §§1.821 to 1.825. This amendment is accompanied by a floppy disk containing the above named sequences, SEQ ID NOS:1-56, in computer readable form, and a paper copy of the sequence information which has been printed from the floppy disk.

The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy. This amendment contains no new matter.

Attached hereto is a marked-up version of the changes made to the Specification and Claims by the current Amendment. The attached pages are captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."** As a convenience to the Examiner, a complete set of the Claims, as amended herein, is also attached to this Amendment as an Appendix entitled **"PENDING CLAIMS WITH ENTRY OF THE AMENDMENT."**

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at line 16 of page 3 has been amended as follows:

FIG. 2 is a graph illustrating the adhesion of MDA-MB-435 breast carcinoma cells to recombinant thrombospondin-1 (TSP1) fragments and TSP1 peptides. Adhesion to synthetic TSP1 peptides adsorbed at 10 μM (Peptide 246~~)~~, KRFKQDGGWSHWSPWSS (SEQ ID NO:1); 500, NGVQYRNC (SEQ ID NO:2); Mal II, SPWSSCSVTCGDGVITRIR (SEQ ID NO:3); 4N1K, KRFYVVMWKK (SEQ ID NO:4); HepI, ELTGAARKGSGRRLVKGPD (SEQ ID NO:5)), TSP1 (0.11 μM), recombinant 18 kDa heparin-binding domain (HBD, 2.7 μM), or GST-fusion proteins expressing the TSP1 procollagen domain, type 1, type 2, type 3 repeats, or GST alone (2 μM) was measured in the absence (solid bars) or presence of 20 μg/ml of the β1 integrin-activating antibody TS2/16 (striped bars). -Results (mean ± SD) are presented for a representative experiment performed in triplicate.

Paragraph beginning at line 26 of page 3 has been amended as follows:

FIGS. 3A and 3B are graphs illustrating the adhesion of MDA-MB-435 breast carcinoma cells to TSP1 peptides and laminin-1 peptide GD6. Panel A: MDA-MB-435 breast carcinoma cell attachment (closed symbols) and spreading (open symbols) was determined on polystyrene substrates coated with the indicated concentrations of TSP1 peptide 678 (FQGVLQNVRFVF (SEQ ID NO:6), circles), TSP1 peptide 701 (TPGQVRTLWHDP (SEQ ID NO:7), squares), or the murine laminin-1 peptide GD6 (KQNCLSSRASFRGCVRNLRLSR (SEQ ID NO:8), triangles). Results are presented as mean ± SD, n = 3. Panel B: Spreading of MDA-MB-435 or MDA-MB-

231 cells on substrates coated with 3.3 μM TSP1 peptide 678, 1.1 μM laminin-1 peptide GD6, or 50 μg/ml TSP1 was determined using untreated cells (solid bars), or cells treated with 5 μg/ml of the β1 activating antibody TS2/16 (gray bars), or 3 nM IGF1 (striped bars, MDA-MB-435 cells only), mean ± SD, n = 3.

Paragraph beginning at line 28 of page 4 has been amended as follows:

FIG. 6 is a histogram showing the determination of the minimal active TSP1 sequence to promote breast carcinoma cell adhesion. MDA-MB-435 cell adhesion was determined to polystyrene coated with 10 μM of the indicated TSP1 peptides (SEQ ID NOS:6, 31, 41, 40, 30, 32, 39 and 56, respectively) or with bovine serum albumin (BSA). Cell attachment is presented as the mean ± SD for triplicate determinations.

Paragraph beginning at line 7 of page 5 has been amended as follows:

FIG. 8 is a histogram showing the effect of systematic substitution of Ala residues on adhesive activities of the TSP1 sequence 190-201 (SEQ ID NOS:6, 25, 26, 27, 29, 10, 42, 11, 44, 43 and 28, respectively) for breast carcinoma cells. Cell attachment was determined to substrates coated with each peptide at 10 μM and is presented as mean ± SD, n = 3. Residues substituted in the native TSP1 sequence are indicated with an asterisk.

Paragraph beginning at line 29 of page 5 has been amended as follows:

FIGS. 11A and 11B display adhesion of endothelial cells on an $\alpha 3\beta 1$ integrin-binding peptide from TSP1. Panel A: TSP1 peptide 678 (FQGVLQNVRFVF; SEQ ID NO:6) or analogs of this peptide with the indicated Ala substitutions (★) were adsorbed on bacteriological polystyrene substrates at 10 μM in PBS. Direct adhesion of BAE cells to the adsorbed peptides or uncoated substrate (control) are presented as mean

± SD, n = 3. Panel B: Loss of cell-cell contact stimulates endothelial cell spreading on TSP1. Two flasks of BAE cells were grown to confluence. One flask was harvested and replated in fresh medium at 25% confluency. Fresh medium was added at the same time to the second flask. After 16 h, cells from both flasks were dissociated using EDTA and adhesion was measured on substrates coated with 40 μg/ml TSP1, 10 μg/ml vitronectin, 20 μg/ml plasma fibronectin, or 5 μg/ml type I collagen. The percent spread cells after 60 min is presented as mean ± SD, n = 3 for a representative experiment.

Paragraph beginning at line 23 of page 6 has been amended as follows:

FIGS. 14A, 14B and 14C display α3β1 and αvβ3 integrin-mediated spreading of endothelial cells on thrombospondin-1. Panel A: BAE cell adhesion to TSP1 (solid bars), vitronectin (striped bars), or plasma fibronectin (open bars) was measured in the presence of 30 μM TSP1 peptide 678, 1 μM of the αvβ3 integrin antagonist SB223245, 300 μM of the integrin antagonist peptide GRGDSP (SEQ ID NO:9), or the indicated combinations. Results are expressed as percent of the response for untreated cells, mean ± S.D., n = 3. Panel B: HUVEC spreading on substrates coated with TSP1 (solid bars) or vitronectin (striped bars) was determined in the presence of 20 μM peptide 678, 1 μM αIIbβ3 antagonist SB208651, 1 μM αvβ3 antagonist SB223245, or 20 μM peptide 678 plus 1 μM SB223245. Spreading is presented as a percent of the respective controls without inhibitors (31 cells/mm2 for TSP1 and 10 cells/mm2 for vitronectin). Panel C: Inhibition of HDME cell spreading on TSP1 (solid bars) or type I collagen (striped bars) was determined in the presence of the indicated function blocking antibodies at 5 μg/ml: anti-CD36 (OKM5), anti-integrin β1 (mAb13), anti-integrin α3 (P1B5), and anti-integrin α4 (P4C2).

Paragraph beginning at line 4 of page 8 has been amended as follows:

FIGS. 19A, 19B, 19C, 19D and 19E display the modulation of endothelial cell proliferation by an $\alpha 3\beta 1$ integrin binding peptide from TSP1. FIG. 19A: Proliferation of BAE cells was assayed in the presence of the indicated concentrations of TSP1 peptide 678 (FQGVLQNVRFVF (SEQ ID NO:6), •) or the control peptides 686 (FQGVLQAVRFVF (SEQ ID NO:10), ▲), and 690 (FQGVLQNVAFVF (SEQ ID NO:11), -O). Briefly, 100 µl of a $5x10^4$ cell/ml suspension of BAE cells were seeded in triplicate into 96 well tissue culture plate in DMEM medium containing 1% FCS, 10 ng/ml of FGF2 and peptides at 1-40 µM concentrations. Cells were incubated for 72 h, and proliferation was measured using the Celltiter tetrazolium assay (Promega). FIG. 19B: HUVE cell proliferation was measured at 72 h for cells plated on wells coated with the indicated concentrations of TSP1 (solid bars) or 1 µg/ml of antibody P1B5 (anti-$\alpha 3\beta 1$ integrin) (striped bar) or P1D6 (anti-$\alpha 5\beta 1$ integrin) in medium 199 containing 5% FCS (striped bar). FIG. 19C: $\alpha 3\beta 1$ integrin mediates the proliferative response to immobilized TSP1. HUVE cells were plated in medium 199 containing 20% FCS on wells coated using 5 µg/ml TSP1, 5 µg/ml vitronectin, or BSA (control) alone or in the presence of 5 µg/ml of the $\alpha 3\beta 1$ blocking antibody P1B5 or 20 µM of TSP1 peptide 678. Proliferation was determined at 72 h, and is presented as a percent of the control, mean ± S.D., n = 3 for experimental points and n = 6 for control. FIG. 19D: HUVE cell proliferation was determined in the presence of the indicated concentrations of TSP1 peptide 678 immobilized on the substrate (solid bars) or added in solution (striped bars). Conditions that significantly differed from their respective controls based on a 2-tailed t test with $p < 0.05$ are marked with an "*". FIG. 19E: HDME cell proliferation in MCDB growth medium with 5% FCS was determined in the presence of 10 ng/ml FGF2 and the indicated concentrations of TSP1 added in the medium (Δ) or immobilized on the substrate ( ) or in wells coated with the indicated concentrations of peptide 678 (▲). Results are presented as mean ± S.D. and are normalized to controls without TSP1 or peptide.

Paragraph beginning at line 22 of page 16 has been amended as follows:

The present invention generally provides peptides, comprising the sequence

$$R_1\text{-}X_1\text{-}X_2\text{-}X_3\text{-}X_4\text{-}R_2 \quad (I)$$

wherein X1 is selected from the group consisting of N, Q, D and S; X2 is selected from the group consisting of V, I and L; X3 is selected from the group consisting of R and K; and X4 is selected from the group consisting of V, I, L and F; R1 is a hydrogen or a peptide of 1 to 6 amino acids, an acyl or an aryl group; and R2 is a peptide of 1 to 3 amino acids, a hydroxide or an amide. In one embodiment of the invention, peptides having the sequence FQGVLQNVRFVF (SEQ ID NO:6) or FRGCVRNLRLSR (SEQ ID NO:12) are specifically excluded. In one embodiment, the peptides contain from 4 to 12 amino acids, i.e., has a length of 4 to 12 amino acid residues. In one embodiment, the peptides comprise additional residues, e.g., typically up to a length of 15, 20, 25, or 40 residues that includes the core sequence (I).

Paragraph beginning at line 1 of page 17 has been amended as follows:

In one embodiment of the present invention, R_1 is a peptide comprising the sequence selected from the group consisting of FQGVLQ (SEQ ID NO:13), FAGVLQ (SEQ ID NO:14), FQGVAQ (SEQ ID NO:15), FQGVLA (SEQ ID NO:16), and FQGVLN (SEQ ID NO:17).

Paragraph beginning at line 4 of page 17 has been amended as follows:

In one embodiment, the peptide of the present invention comprises at least one sequence selected from the group consisting of FQGVLQNLRFVF (SEQ ID NO:18), FQGVLQDVRFVF (SEQ ID NO:19), FQGVLQQVRFVF (SEQ ID NO:20), FQGVLQSVRFVF (SEQ ID NO:21), acQGVLQNVRF (SEQ ID NO:22),

FQGVLQNVKFVF (SEQ ID NO:23), -FQGVLNNVRFVF (SEQ ID NO:24), AQGVLQNVRFVF (SEQ ID NO:25), FAGVLQNVRFVF (SEQ ID NO:26), FQGVAQNVRFVF (SEQ ID NO:27), FQGVLQNVRFVA (SEQ ID NO:28), FQGVLANVRFVF (SEQ ID NO:29), FQGVLQNVRFV (SEQ ID NO:30), QGVLQNVRFVF (SEQ ID NO:31), FQGVLQNVRF (SEQ ID NO:32), and FQGVLQNVRFVF (SEQ ID NO:6).

Paragraph beginning at line 31 of page 25 has been amended as follows:

The peptide GRGDSP (SEQ ID NO:9) was obtained from Gibco/BRL. A non-peptide antagonist of αv integrins was provided by Dr. William H. Miller (SmithKline Beecham Pharmaceuticals, King of Prussia, PA) (Keenan, 1997).

Paragraph beginning at line 24 of page 30 has been amended as follows:

A multiple alignment search using MACAW software was used to identify TSP1 sequences that might be related to the $\alpha 3\beta 1$ integrin-binding murine laminin-1 peptide KQNCLSSRASFRGCVRNLRLSR (GD6 peptide; SEQ ID NO:8) derived from the A chain of murine laminin-1 (Gehlsen et al., 1992), which strongly promoted MDA-MB-435 cell adhesion (**FIG. 3A**). This search identified four TSP1 sequences related to the laminin peptide (**Table 1**).

Paragraph (**Table 1.**) beginning at line 1 of page 31 has been amended as follows:

Table 1. TSP1 sequences related to murine laminin-1 peptide GD6.

The amino acid sequences for human and murine TSP1 and laminin-1 peptide GD6 were compared by multiple alignment using MACAW. Alignment scores were determined by segment pair overlap or Gibbs sampler (*) methods.

Peptide origin	sequence	MP score vs. GD6	p value	SEQ ID NO:
laminin GD6	KQNCLSSRASFRGCVRNLRLSR	-	-	8
laminin p679	FRGCVRNLRLSR	-	-	12
TSP1(598-608)	NCLPCPPRFTG	42.0	5.9x10-8	33
TSP1(188-199)	DNFQGVLQNVRF	39.0	5.9x10-7	34
TSP1(392-405)	NNRCEGSSVQTRTC	35.0	4.5x10-4	35
TSP1(1059-1077)	RNALWHTGNTPGQVRTLWH	43.3*	2.1x10-8	36

Paragraph (**Table 2.**) beginning at line 8 of page 33 has been amended as follows:

Table 2. Inhibition of MDA-MB-435 cell adhesion to immobilized peptide 678 by peptide analogs of TSP1 as well as direct adhesion of immobilized peptide analogs to MDA-MB-435 cells.

Mean doses to achieve 50% inhibition of control adhesion (IC_{50}) to polystyrene coated with 5 μM peptide 678 were determined from at least three independent experiments, each performed in triplicate. Peptides were tested at up to 300 μM or to the solubility limit for each peptide where lower limits for inhibitory activity are indicated.

#	Sequence (SEQ ID NO:)	MW	Source	Inhibition of peptide 678 (IC_{50})	Direct adhesion#
674	GEFYFDLRLKGDKY (37)	1751	type IV coll.		
675	KQNCLSSRASFRGCVRNLRLSR (8)	2552	laminin GD6		+++
678	FQGVLQNVRFVF (6)	1454	TSP1	3.5((15))	+++
679	FRGCVRNLRLSR (12)	1477	part of GD6	((700))	+++
681	ac-LQNVRF-am (38)	815	part of 678	500	-
682	FQGVLQNVRF (32)	1207		6	++
683	QGVLQNVR (39)	913		>300	-
685	QGVLQNVRFVF (31)	1307		24	++
684	LQNVRFVF (40)	1022		300	+/-
688	VLQNVRFVF (41)	1121		>100	+
689	FQGVLQNVRFV (30)	1307		+	+
686	FQGVLQAVRFVF (10)	1411		>300	++
687	FQGVLANVRFVF (29)	1397		3	++
690	FQGVLQNVAFVF (11)	1369		>300	-
691	FQGVLQNARFVF (42)	1426		>300	++
692	FQGVLQNVRAVF (43)	1378		18	++
693	FQGVLQNVRFVA (28)	1378		27	++
694	FQGVLQNVHFVF (44)	1435		54	+/-
695	FQGVAQNVRFVF (27)	1412		5	++
696	FAGVLQNVRFVF (26)	1397		1.8((12))	++
697	AQGVLQNVRFVF (25)	1378		5	++
698	FQGVLNNVRFVF (24)	1440		3	++
701	TPGQVRTLWHDP (7)	1407	(part of C6)	>300	-
702	FQGVLQNVKFVF (23)	1426		6((25))	+++
703	FQGVLQNVQFVF (45)	1426		>100((300))	+/-
704	acQGVLQNVRF (22)	1060		15((~100))	++
705	FQGVLQSVRFVF (21)	1427		((15))	++
709	D reverse-678 (-)			((18))	
716**	carboxamidomethyl-thioproprionyl-FQGVLQNVRFVF (46)	~~MW~~ 1538		((100))	
717	FQGVLQQVRFVF (20)	1468		((30))	
718	FQGVLQDVRFVF (19)	1455		((12))	
719	FQGVLQNLRFVF (18)	1468		((16))	

* Inhibition constants (IC_{50}) were determined by microscopic adhesion assays except where indicated by (()) in which case the inhibition constants were determined by the hexosaminidase hexosamindase method.

#Activity to promote MDA-MB-435 cell adhesion in a direct adhesion assay using peptides adsorbed on polystyrene.

Paragraph (**Table 3.**) beginning at line 1 of page 36 has been amended as follows:

Table 3. Mapping of essential residues for inhibition of MDA-MB-435 cell adhesion to immobilized peptide 678.

Mean doses to achieve 50% inhibition of control adhesion to 5 μM peptide 678 (IC_{50}) were determined from at least three independent experiments, each performed in triplicate. Residues substituted in the native TSP1 sequence are underlined. substituted in the native TSP1 sequence are underlined.

Peptide	Sequence	SEQ ID NO:	IC_{50} (μM)
678	FQGVLQNVRFVF (TSP1)	6	3.5
697	AQGVLQNVRFVF	25	5
696	FAGVLQNVRFVF	26	1.8
695	FQGVAQNVRFVF	27	5
687	FQGVLANVRFVF	29	3
686	FQGVLQAVRFVF	10	>300
691	FQGVLQNARFVF	42	>300
690	FQGVLQNVAFVF	11	>300
702	FQGVLQNVKFVF	23	6
694	FQGVLQNVHFVF	44	54
703	FQGVLQNVQFVF	45	>100
692	FQGVLQNVRAVF	43	18
693	FQGVLQNVRFVA	28	27

Paragraph beginning at line 22 of page 37 has been amended as follows:

Based on examination of synthetic peptides and recombinant fragments representing approximately 90% of the TSP1 sequence, only the sequence FQGVLQNVRFVF (SEQ ID NO:6) from the amino terminal domain exhibited activities

that are expected for an $\alpha 3\beta 1$ integrin binding sequence in TSP1. A recombinant fragment of TSP1 containing this sequence also promoted $\beta 1$ integrin-dependent adhesion. In solution, this peptide specifically inhibited adhesion to TSP1 but not to ligands recognized by other integrins. Adhesion to this peptide and to TSP1 was stimulated by IGF1 receptor ligands that stimulate integrin-dependent adhesion to intact TSP1, by Mn^{2+}, and by a $\beta 1$ integrin-activating antibody and partially inhibited by an $\alpha 3\beta 1$ function blocking antibody. Based on systematic amino acid substitutions in the active sequence, NVR appears to be the essential core sequence in this TSP1 peptide for recognition by the $\alpha 3\beta 1$ integrin.

Paragraph beginning at line 33 of page 37 has been amended as follows:

Adhesive activities of the immobilized peptides imply that only Arg(198) may directly participate in this interaction, although the partial resistance to inhibition by an $\alpha 3\beta 1$ integrin antibody and EDTA suggest that the peptides with Arg may also support adhesion independent of integrin binding. The context surrounding the Arg is important, however, because other peptides with similar sequences (such as peptide 701 with a QVRT (SEQ ID NO:47) sequence) had no activity, and Ala substitutions of the flanking residues in peptide 678 eliminated or markedly decreased its inhibitory activity in solution. The essential amino acid residues are completely conserved in human, murine, bovine, and Xenopus TSP1, although in chicken TSP1 a His replaces the Arg. A similar motif is found in murine and human TSP2, with a His residue replacing the Arg. As a free peptide the TSP1 sequence with a His substitution was much less active, so it is not clear whether the TSP2 sequence could be recognized by $\alpha 3\beta 1$integrin. Activity of the latter sequence may be increased in an environment that increases protonation of the imidazole in His.

Paragraph beginning at line 12 of page 38 has been amended as follows:

A consensus $\alpha 3\beta 1$ integrin recognition sequence in $\alpha 3\beta 1$ ligands has not been reported. One hypothesis is that different ligands have unrelated binding sequences, which is supported by a recent mutagenesis study (Krukonis et al., 1998). However, other recent data has raised questions about whether all of the proteins reported to mediate $\alpha 3\beta 1$-dependent adhesion are true $\alpha 3\beta 1$ ligands (Krukonis et al., 1998). LamA2 and LamA3 were verified to bind $\alpha 3\beta 1$ integrin and have potential binding motifs based on the data, but human LamA1, which was found not to bind $\alpha 3\beta 1$ with high avidity, has an Ala in the position occupied by the essential Arg in the TSP1 sequence. Substitution of Ala for the Arg in the TSP1 sequence abolished all activity of the synthetic TSP1 peptide. Although RGD was reported to be an $\alpha 3\beta 1$ ligand, the RGD in entactin is not required for recognition. A binding site for the $\alpha 3\beta 1$ integrin in entactin was mapped to the G2 domain (residues 301-647) (Gresham et al., 1996). Multiple alignment of this region of entactin against the TSP1 sequence and the murine laminin-1 peptide GD6 identified a related sequence FSGIDEHGHLTI (SEQ ID NO:48), but this sequence lacks any of the essential residues in the TSP1 sequence. This domain of entactin also contains two NXR sequences: NNRH (SEQ ID NO:49) and NGRQ (SEQ ID NO:50). It remains to be determined whether either of these can function as an $\alpha 3\beta 1$ integrin recognition sequence.

Paragraph beginning at line 11 of page 41 has been amended as follows:

The increased spreading of BAE cells on TSP1 is mediated at least in part by $\alpha 3\beta 1$ integrin, because a TSP1 peptide that binds to this integrin inhibited spreading on TSP1 by 55% but did not inhibit spreading on fibronectin or vitronectin substrates (**FIG. 14A**). The $\alpha v\beta 3$ integrin also plays some role in BAE cell spreading on TSP1, since the αv integrin antagonist SB223245 partially inhibited spreading on TSP1. The effect of these two inhibitors was additive, producing a 76% inhibition of spreading when

combined. Similar results were obtained using the $\alpha v\beta 3$ peptide antagonist GRGDSP (SEQ ID NO:9) alone and in combination with peptide 678. Approximately 20% of the spreading response on TSP1 was resistant to the GRGDSP (SEQ ID NO:9) peptide, but combining this peptide with the $\alpha 3\beta 1$ binding peptide completely inhibited spreading on TSP1.

Paragraph beginning at line 30 of page 46 has been amended as follows:

The $\beta 1$ integrin recognition sequence in TSP1 may also contribute to angiogenesis, because peptide 678 (FQGVLQNVRFVF; SEQ ID NO:6) inhibited angiogenesis in the CAM assay (**Table 5**). The results of dose dependent inhibition of angiogenic response for various peptides (including peptide 678) are presented in **Table 5**.

Paragraph (**Table 5.**) beginning at line 1 of page 47 has been amended as follows:

Table 5. Angiogenetic response (% inhibition) of various peptides determined by chick chorioallantoic membrane (CAM) angiogenesis assay.

Vitrogen gels containing peptides at the indicated concentrations were placed on CAMs in triplicate. Angiogenesis was assessed by injecting FITC-dextrans after 24 h and imaging the resulting vascular bed in the gels. Results are presented as percent inhibition relative to control gels without peptides, mean ± SD.

Peptide	SEQ ID NO:	5 μM	10 μM	20 μM
FQGVLQNVRFVF	6	2 ± 5	17 ± 7	37 ± 9
FQGVLQAVRFVF	10	3 ± 4	4 ± 6	15 ± 7
FQGVLQNVAFVF	11	3 ± 3	5 ± 3	2 ± 5
FAGVLQNVRFVF	26	5 ± 2	9 ± 3	12 ± 4
D-ri-FQGVLQNVRFVF	-	5 ± 4	25 ± 13	39 ± 13

In the Claims:

Claims 1, 3, 4 and 5 have been amended as follows:

1. (Amended) A peptide comprising the sequence R_1-X_1-X_2-X_3-X_4-R_2, wherein X_1 is selected from the group consisting of N, Q, D and S; X_2 is selected from the group consisting of V, I and L; X_3 is selected from the group consisting of R and K; and X_4 is selected from the group consisting of V, I, L and F; R_1 is a hydrogen or a peptide of 1 to 6 amino acids, an acyl or an aryl group; and R_2 is a peptide of 1 to 3 amino acids, a hydroxide or an amide, provided that the peptide does not comprise the sequence FQGVLQNVRFVF (SEQ ID NO:6) or FRGCVRNLRLSR (SEQ ID NO:12).

3. (Amended) The peptide of claim 1 wherein R_1 is a peptide comprising the sequence selected from the group consisting of FQGVLQ (SEQ ID NO:13), FAGVLQ (SEQ ID NO:14), FQGVAQ (SEQ ID NO:15), FQGVLA (SEQ ID NO:16), and FQGVLN (SEQ ID NO:17).

4. (Amended) The peptide of claim 1 peptide comprising at least one sequence selected from the group consisting of FQGVLQNLRFVF (SEQ ID NO:18), FQGVLQDVRFVF (SEQ ID NO:19), FQGVLQQVRFVF (SEQ ID NO:20),

FQGVLQSVRFVF (SEQ ID NO:21), acQGVLQNVRF (SEQ ID NO:22), FQGVLQNVKFVF (SEQ ID NO:23), -FQGVLNNVRFVF (SEQ ID NO:24), AQGVLQNVRFVF (SEQ ID NO:25), FAGVLQNVRFVF (SEQ ID NO:26), FQGVAQNVRFVF (SEQ ID NO:27), FQGVLQNVRFVA (SEQ ID NO:28), FQGVLANVRFVF (SEQ ID NO:29), FQGVLQNVRFV (SEQ ID NO:30), QGVLQNVRFVF (SEQ ID NO:31), and FQGVLQNVRF (SEQ ID NO:32), ~~and FQGVLQNVRFVF~~.

PENDING CLAIMS WITH ENTRY OF THE AMENDMENT

1. (Amended) A peptide comprising the sequence R_1-X_1-X_2-X_3-X_4-R_2, wherein X_1 is selected from the group consisting of N, Q, D and S; X_2 is selected from the group consisting of V, I and L; X_3 is selected from the group consisting of R and K; and X_4 is selected from the group consisting of V, I, L and F; R_1 is a hydrogen or a peptide of 1 to 6 amino acids, an acyl or an aryl group; and R_2 is a peptide of 1 to 3 amino acids, a hydroxide or an amide, provided that the peptide does not comprise the sequence FQGVLQNVRFVF (SEQ ID NO:6) or FRGCVRNLRLSR (SEQ ID NO:12).

2. (As filed) The peptide of claim 1 containing from about 4 to about 12 amino acids.

3. (Amended) The peptide of claim 1 wherein R_1 is a peptide comprising the sequence selected from the group consisting of FQGVLQ (SEQ ID NO:13), FAGVLQ (SEQ ID NO:14), FQGVAQ (SEQ ID NO:15), FQGVLA (SEQ ID NO:16), and FQGVLN (SEQ ID NO:17).

4. (Amended) The peptide of claim 1 peptide comprising at least one sequence selected from the group consisting of FQGVLQNLRFVF (SEQ ID NO:18), FQGVLQDVRFVF (SEQ ID NO:19), FQGVLQQVRFVF (SEQ ID NO:20), FQGVLQSVRFVF (SEQ ID NO:21), acQGVLQNVRF (SEQ ID NO:22), FQGVLQNVKFVF (SEQ ID NO:23), FQGVLNNVRFVF (SEQ ID NO:24), AQGVLQNVRFVF (SEQ ID NO:25), FAGVLQNVRFVF (SEQ ID NO:26), FQGVAQNVRFVF (SEQ ID NO:27), FQGVLQNVRFVA (SEQ ID NO:28), FQGVLANVRFVF (SEQ ID NO:29), FQGVLQNVRFV (SEQ ID NO:30), QGVLQNVRFVF (SEQ ID NO:31), and FQGVLQNVRF (SEQ ID NO:32).

5. (Amended) The peptide of claim 1 wherein X_1-X_2-X_3-X_4 is selected from the group consisting of NVRF (SEQ ID NO:51), SVRF (SEQ ID NO:52), QVRF (SEQ ID NO:53), DVRF (SEQ ID NO:54) and NLRF (SEQ ID NO:55).

6. (As filed) The peptide of claim 1 that is selected from the group consisting of partial and full retro-inverso peptide sequences.

7. (As filed) The peptide of claim 6 that comprises at least one D-amino acid.

8. (As filed) A retro-inverso synthetic peptide comprising the amino acids sequence, from C-terminal (left) to N-terminal (right): ri- R'_1-X'_1-X'_2-X'_3-X'_4-R'_2, wherein ri denotes a retro-inverso peptide and all amino acids are D amino acids; X'_1 is selected from the group consisting of N, Q, D and S; X_2 is selected from the group consisting of V, I and L; X_3 is selected from the group consisting of R and K; and X_4 is selected from the group consisting of V, I, L and F; R'_1 is a hydrogen or a peptide of 1 to 6 amino acids, a hydroxide or an amide; and R'_2 is a peptide of 1 to 3 amino acids, an acyl or an aryl group.

9. (As filed) The peptide of claim 8 containing from about 4 to about 12 amino acids.

10. (As filed) The peptide of claim 6 comprising the sequence FQGVLQNVRFVF wherein every amino acid in said sequence is a D-amino acid.

11. (As filed) A peptide-substrate combination comprising a substrate suitable for cell growth and a peptide of 4 to 12 amino acids attached to said substrate, said peptide comprising the sequence R_1-X_1-X_2-X_3-X_4-R_2, wherein X_1 is selected from the group consisting of N, Q, D and S; X_2 is selected from the group consisting of V, I

and L; X_3 is selected from the group consisting of R and K; and X_4 is selected from the group consisting of V, I, L and F; R_1 is a hydrogen or a peptide of 1 to 6 amino acids, an acyl or an aryl group; and R_2 is a peptide of 1 to 3 amino acids, a hydroxide or an amide.

12. (As filed) The substrate of claim 11 that is a cell culture substrate.

13. (As filed) A pharmaceutical composition comprising a peptide and a pharmaceutically acceptable carrier, said peptide comprising the sequence R_1-X_1-X_2-X_3-X_4-R_2, or partial or full retro-inverso sequences thereof, wherein X_1 is selected from the group consisting of N, Q, D and S; X_2 is selected from the group consisting of V, I and L; X_3 is selected from the group consisting of R and K; and X_4 is selected from the group consisting of V, I, L and F; R_1 is a hydrogen or a peptide of 1 to 6 amino acids, an acyl or an aryl group; and R_2 is a peptide of 1 to 3 amino acids, a hydroxide or an amide.

14. (As filed) A sterile composition comprising a peptide and a sterile aqueous solution, said peptide comprising the sequence R_1-X_1-X_2-X_3-X_4-R_2, or partial or full retro-inverso sequences thereof, wherein X_1 is selected from the group consisting of N, Q, D and S; X_2 is selected from the group consisting of V, I and L; X_3 is selected from the group consisting of R and K; and X_4 is selected from the group consisting of V, I, L and F; R_1 is a hydrogen or a peptide of 1 to 6 amino acids, an acyl or an aryl group; and R_2 is a peptide of 1 to 3 amino acids, a hydroxide or an amide.

15. (As filed) A peptide conjugate comprising a peptide and a water soluble polymer, said peptide comprising the sequence R_1-X_1-X_2-X_3-X_4-R_2, or partial or full retro-inverso sequences thereof, wherein X_1 is selected from the group consisting of N, Q, D and S; X_2 is selected from the group consisting of V, I and L; X_3 is selected from the group consisting of R and K; and X_4 is selected from the group consisting of V, I, L and F; R_1 is a hydrogen or a peptide of 1 to 6 amino acids, an acyl or an aryl group; and

R_2 is a peptide of 1 to 3 amino acids, a hydroxide or an amide; and a water soluble polymer.

16. (As filed) The peptide conjugate of claim 15 wherein the water soluble polymer comprises at least one member selected from the group consisting of polysucrose and dextran.

17. (As filed) The peptide-substrate combination of claim 11 wherein the substrate comprises metal, glass, glass fiber, ceramic, polystyrene, polyethylene, cellulose, nylon, polycarbonate, polyurethane, polyester, tetrafluoroethylene polymer , or silicone rubber.

18. (As filed) A vascular graft comprising the peptide-substrate combination of claim 11.

19. (As filed) An artificial blood vessel comprising the peptide-substrate combination of claim 11.

20. (As filed) A method of inhibiting adhesion of a cell expressing $\alpha 3\beta 1$ integrin to an extracellular matrix comprising contacting said cell with a peptide comprising the sequence R_1-X_1-X_2-X_3-X_4-R_2, or partial or full retro-inverso sequences thereof; wherein X_1 is selected from the group consisting of N, Q, D and S; X_2 is selected from the group consisting of V, I and L; X_3 is selected from the group consisting of R and K; and X_4 is selected from the group consisting of V, I, L and F; R_1 is a hydrogen or a peptide of 1 to 6 amino acids, an acyl or an aryl group; and R_2 is a peptide of 1 to 3 amino acids, a hydroxide or an amide.

21. (As filed) The method of claim 20 wherein the extracellular matrix comprises TSP1 or laminins.

22. (As filed) The method of claim 20 wherein said contacting takes place *in vitro*.

23. (As filed) The method of claim 20 wherein said cell comprises an epithelial or an endothelial cell.

24. (As filed) The method of claim 20 wherein said cell is a tumor cell.

25. (As filed) The method of claim 20 wherein said cell is a breast carcinoma cell or a small cell lung carcinoma.

26. (As filed) A method of inhibiting $\alpha 3\beta 1$ integrin-mediated cell motility, comprising contacting a cell with a peptide comprising the sequence R_1-X_1-X_2-X_3-X_4-R_2, or partial or full retro-inverso sequences thereof; wherein X_1 is selected from the group consisting of N, Q, D and S; X_2 is selected from the group consisting of V, I and L; X_3 is selected from the group consisting of R and K; and X_4 is selected from the group consisting of V, I, L and F; R_1 is a hydrogen or a peptide of 1 to 6 amino acids, an acyl or an aryl group; and R_2 is a peptide of 1 to 3 amino acids, a hydroxide or an amide.

27. (As filed) The method of claim 26 wherein said contacting occurs *in vitro*.

28. (As filed) The method of claim 26 wherein the cell is an epithelial cell, an endothelial cell or a malignant cell.

29. (As filed) A method of inhibiting proliferation of endothelial cells, comprising contacting said cells with a peptide comprising the sequence R_1-X_1-X_2-X_3-X_4-R_2, or partial or full retro-inverso sequences thereof; wherein X_1 is selected from the group consisting of N, Q, D and S; X_2 is selected from the group consisting of V, I and

L; X_3 is selected from the group consisting of R and K; and X_4 is selected from the group consisting of V, I, L and F; R_1 is a hydrogen or a peptide of 1 to 6 amino acids, an acyl or an aryl group; and R_2 is a peptide of 1 to 3 amino acids, a hydroxide or an amide.

30. (As filed) A method of inhibiting proliferation of small cell lung carcinoma, comprising contacting said cell with a peptide of 4 to 12 amino acids comprising the sequence R_1-X_1-X_2-X_3-X_4-R_2, or partial or full retro-inverso sequences thereof; wherein X_1 is selected from the group consisting of N, Q, D and S; X_2 is selected from the group consisting of V, I and L; X_3 is selected from the group consisting of R and K; and X_4 is selected from the group consisting of V, I, L and F; R_1 is a hydrogen or a peptide of 1 to 6 amino acids, an acyl or an aryl group; and R_2 is a peptide of 1 to 3 amino acids, a hydroxide or an amide.

31. (As filed) A method of promoting the proliferation of an endothelial cell, comprising contacting said cell with the peptide-substrate combination of claim 11 under conditions supportive of cell division.

32. (As filed) The method of claim 31 wherein said contacting takes place *in vitro*.

33. (As filed) The method of claim 31 wherein the endothelial cell is a human cell.

34. (As filed) The method of claim 31 wherein said contacting takes place in an animal.

35. (As filed) The method of claim 31 wherein said contacting takes place in an animal. The method of claim 34 wherein said contacting occurs in the wall of a blood vessel.

36. (As filed) The method of claim 34 wherein the animal is a rat, mouse, human or a non-human primate.

37. (As filed) A method of treating an angiogenesis-mediated disease in an animal comprising administering to the animal an effective amount of a peptide comprising the sequence R_1-X_1-X_2-X_3-X_4-R_2, or partial or full retro-inverso sequences thereof; wherein X_1 is selected from the group consisting of N, Q, D and S; X_2 is selected from the group consisting of V, I and L; X_3 is selected from the group consisting of R and K; and X_4 is selected from the group consisting of V, I, L and F; R_1 is a hydrogen or a peptide of 1 to 6 amino acids, an acyl or an aryl group; and R_2 is a peptide of 1 to 3 amino acids, a hydroxide or an amide.

38. (As filed) The method of claim 37 wherein the angiogenesis-mediated disease is diabetic retinopathy, retinopathy of prematurity, rheumatoid arthritis, macular degeneration, atherosclerosis plaque formation, or a cancer.

39. (As filed) The method of claim 37 wherein the animal is a rat, mouse, human or nonhuman primate.

40. (As filed) The method of claim 37 wherein the disease is cancer.

41. (As filed) The method of claim 40 wherein the cancer is characterized by the formation of a solid tumor.

42. (As filed) The method of claim 41 wherein said solid tumor tissue is a carcinoma.

43. (As filed) The method of claim 37 wherein the administration is intravenous, transdermal, intramuscular, topical, subcutaneous, intracavity, or peristaltic administration.

44. (As filed) A method of inducing solid tumor tissue regression in a patient comprising administering to said patient a composition sufficient to inhibit neovascularization of said solid tumor tissue, said composition comprising a peptide, said peptide comprising the sequence R_1-X_1-X_2-X_3-X_4-R_2, or a partial or full retro-inverso sequences thereof; wherein X_1 is selected from the group consisting of N, Q, D and S; X_2 is selected from the group consisting of V, I and L; X_3 is selected from the group consisting of R and K; and X_4 is selected from the group consisting of V, I, L and F; R_1 is a hydrogen or a peptide of 1 to 6 amino acids, an acyl or an aryl group; and R_2 is a peptide of 1 to 3 amino acids, a hydroxide or an amide.

45. (As filed) The method of claim 44 wherein said administering is conducted in conjunction with chemotherapy or radiotherapy.